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SILICON-BASED MULTISENSOR MICROSYSTEM

[MICROSISTEMA MULTISENSOR BASADO EN SILICIO]

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DESCRIPTION

Silicon-based Multisensor Microsystem

Technical sector

This invention falls within the semiconductor technology sector with respect to the manufacturing process and in the medical sector with respect to its application.

Technical status

In recent years, a large number of sensors based on microelectronic technology have been developed. Among these, the ion sensitive field effect transistor (ISFET) is widely known. Said device is basically a Metal-Oxide Semiconductor (MOS) transistor in which the gate's metal has been replaced with an ion solution that contains the ion to be analyzed.

Patents such as U.S. patent 40208830 use one of these transducers (chemical sensitive field-effect transistors) to detect and measure the chemical properties of the substances to which the transducer is exposed.

U.S. patent 5387328 (SENSOR TECHNOLOGY RESEARCH CENTER OF KYUNGPOOK NATIONAL UNIVERSITY - Bio-Sensor Using Ion Sensitive field effect transistor with platinum electrode) again uses the ISFET sensor, this time to obtain a biosensor capable of

[1] Numbers in the margin indicate pagination in the foreign text.

measuring glucose, and adds a Pt electrode to increase the sensitivity and reduce the sensor's reaction time.

There are also other patents that propose using a multisensor device, such as U.S. patent number 4874500 (SRI International - Microelectrochemical sensor and sensor array). In this patent, a series of amperometric electrodes are used to measure CO_2, O_2, K^+ and W^+. The measurement method used in this patent is different from the measurement method proposed in the patent herein because it uses an amperometric method, amperometric electrodes, instead of ISFET-based conductimetric sensors. Column 1, lines 27 to 50 of this patent explain the number of problems ISFET sensors have with respect to stability, manufacture and obtaining the referenced electrode. Said problems are resolved in our invention. Another difference found is the type of application, because it is not possible to make dynamic measurements. In this patent it is suggested that the system could be provided with an integrated circuit to amplify or deal with the signal, but said circuit is not described.

Another of the patents referenced in the report regarding technical status is U.S. patent number 5394883 (CASE WESTERN RESERVE UNIVERSITY - Multiple Thin Film Sensor System). This patent involves an airflow sensor that uses thermoresistances. It determines the flow by the difference in the temperatures between the air injected and that of the ambient air. The sensors used are thermoresistances and the application attempts to monitor the

airflow of a person's respiration. They use different thermoresistances (sometimes they need to heat the air before measuring the flow) but to take a single type of measurement, airflow measurement, and it is, therefore, not a multisensor system. This invention, therefore, has a different application, technology and totally different sensors from that proposed in the patent herein.

U.S. patent 5393401 (Knoll, M. - Method of manufacturing miniaturized components of chemical and biological detection sensors that employ ion-selective membranes, and supports for such components) describes a method for manufacturing miniature components of biological and chemical detection sensors and the supports for said components.

U.S. patent 5846392 (Knoll, M - Miniaturized circulatory measuring chamber with integrated chemo- and/or bio-sensor elements) describes a microfluidic job. The structure presented, contrary to what is intended to patent, is not superficial but rather a circulatory chamber with a series of conduits. The application and manufacturing process of these two inventions are, consequently, different.

Finally, U.S. patent 538659 (SIEMENS - reference electrode) describes a flat reference electrode for chemical sensors. It is widely known that the ISFET sensor needs a reference electrode to polarize the device's gate and to be able to perform its sensor function. This patent proposes a reference electrode that can be

a metal or a sensor, preferably an ISFET sensor and coated with a polymer. The differences noted are that the patent herein claims to use a metal reference electrode (because it is required in order to use the ISFET as a sensor) and, therefore, uses

/3[2]

different manufacturing processes to integrate it with the rest of the system's elements. Additionally, it does not use the diffusion system through polymer layers described in U.S. patent 5385659.

The following cites a series of groups that work in developing systems with a certain similarity to the invention in this document.

Author	Center	Characteristics	Differences with microcard
Kenneth S. Szajda, H. Frederick Bowman, Charles G. Sodini	Harvard-MIT Division of Health Sciences and Technology (HST)	Microchip with temperature sensor. Provides adding radiation and oxygen sensors. Application: cancer treatment	• The sensors (microchips) are encapsulated within one needle and do not share the same substratum.

[2] Numbers in the margin indicate pagination in the foreign text.

		by hyperthermia.	
Khalil Najafi, Kensall Wise	Dept. of Electrical Engineering and Computer Science, University of Michigan	Silicon Multichannel Recording probes	• Only platinum points. • Records neutral signals or stimulation. • No telemetry.
Andre Dittmar	National Scientific Research Center (CNRS). Faculty of Medicine. Lyon, France.	Biomedical multi-microcapture: 30 parameters and variables to typify (metabolic activity) live tissues: micro-circulation, temperature, conductivity, glucose, lactate, pyruvate, po2, NO, etc.	• Does not record electric impedance. • CFME-based chemical sensors (carbon fiber micro-electrode), not ISFET based. • Does not record K^+ or pH. • Telemetry has not been proposed (?).

Richard Buck, Vasile Cosofret... Neuman	Dept. of Chemistry, Univ. of North Carolina. + Univ. of Budapest + Cleveland Medical Center	Potenciometric ion-sensitive planar microelectrode arrays and amperometric enzyme-containing biosensors. Polymide substratum. H+, K+, Na+, Ca2+	• ISE sensors (not ISFET) • Does not measure impedance. • Polymide substratum. • Prototype has no telemetry.
Marcelo V.A. Fontes; Jorge Santiago Aviles; Rogerio Furlan	LSI/University of Sao Paulo (Brazil), University of Pennsylvania (U.S.A.)	Electrode array in planar technology for making amperometric sensors (electro-chemical sensors).	• Amperometric sensors (ISFET are potencio-metric). • Does not measure impedance. • No telemetry.

Description of the invention

Short description of the invention

The novelty is that the invention is a silicon-based multisensor microsystem of reduced dimensions, approximately millimeters, (a model could have the approximate dimensions 8 x 1.1 x 0.5 mm), whose shape is similar to a needle with one end or head of a larger thickness. In the straight section, there is a series of sensors. One possible model includes a K+ sensor, a pH sensor and a temperature sensor, and four platinum electrodes.

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Its shape makes it possible to insert it in tissues or organs, and the device's anchor can also be inserted in the tissue. Low power/low noise circuits are connected at the proximal or widest part to handle and regulate the signals, as well as the telemetry circuitry for transmitting these data.

The system is also applicable for measuring other types of ions, Na+, Ca2+, etc.

Its usefulness is for continuous and simultaneous monitoring of changes in impedance, ion concentration such as extracellular K+, and also pH and the temperature of tissues, organs or body liquids.

The invention's innovation is its compatibilization of technologies and the development of technological processes in

[3] Numbers in the margin indicate pagination in the foreign

silicon, which enables simultaneous incorporation in the same microsystem of different signal-capturing elements, as well as its suitability for biomedical use.

Detailed description of the invention

As shown schematically in figure 1, the lancet consists of a thin silicon needle in which four pairs of platinum electrodes are located for measuring impedances, along with four ISFET devices sensitive to the hydrogen ion (H+) concentration, because the gate's insulation is the inorganic material silicon nitride (Si_3N_4). These materials placed in the form of thin layers can also serve as substrata for the placement of polymeric membranes sensitive to a certain type of ion. The devices obtained with the incorporation of these membranes are called MEMFETs (Membrane Field-Effect: Transistor). Therefore, a potassium ion discriminating membrane will be placed in one of the ISFETs and in the other a membrane insensitive to pH and pK, for the purpose of taking differential measurements of the H+ and K+ concentrations. One or two of these lancets, according to the model, will be encapsulated in silicon, along with adequate preamplification circuitry and signal conditioning, multiplexation and telemetry to transmit the measurements taken to a multichannel receptor system located at a distance of 1 to 5 meters.

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text.

Technology of the biosensors

pH sensor

Ion-sensitive field effect transistors (ISFET) are used, in other words, solid state pH sensitive chemical sensors where the oxide-electrolyte (ψ_0) interface potential is used to modulate a resistance that along with the potential applied to the drain in relationship to the source (V_{ds}) determines the value of the I_{ds} current that circulates between the drain and the source, and, therefore, the I_{ds} will vary with the concentration of the solution.

NMOS technology compatible with the CMOS technology of the National Microelectric Center is used. The mask levels are 7.

It is based on p-type (100), boron-doped silicon wafers. Two doping regions are formed in this substratum, different from that pertaining to the silicon, source and drain. The first step is to oxidize the field as a protective layer for selective diffusion of the source and the drain. Phosphorus is introduced to form the source and drain regions (n+). Photolythography and etching the oxide, defining the ISFET gate (canal). The gates thin oxide increases. Deposition of a silicon nitrite layer (inorganic membrane sensitive to pH, Si_3N_4), photolythography and etching.

Deposition of the platinum (Lift-Off) to constitute the reference electrode that will polarize the device.

Passivation to protect the device and gate opening and

contacts.

Define the lancet using an aluminum layer as a mask.

Aluminum deoxidation.

K+ sensor

A MEMFET device is used. The MEMFET modifies the structure of the ISFET. This modification consists of depositing a polymeric membrane in the active region of the ISFET gate in order to obtain a device sensitive to a determined ion. In our case, the device is K+ sensitive.

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Platinum electrode

The Pt electrode to measure impedance and the Pt electrode that acts as a reference electrode are made according to the same process as that indicated in the case of the pH sensor.

Integrated circuit to acquire data and telemetry

The integrated circuit handles generating the signals needed to stimulate the electrodes and biosensors, record the measurements acquired and establish the responses of the electrodes and biosensors.

To take the impedance measurements, an alternating current is applied through the external electrodes and determines the phase components and quadrature of the internal electrode tension

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[4] Numbers in the margin indicate pagination in the foreign text.

drop. Figures 16 to 22 show a detailed model of this circuit, with the understanding that the circuit's topology can vary and does not have to be that shown in this example.

In a very similar way, specific signals are applied to the ISFET in order to obtain readings of the pH, K+ concentration or some other type of concentration one wants to measure.

The output signals will be digitized by an A/D converter and sent to the external instrumentation. When the application allows, use of the telemetry system can be avoided, and instead a physical connection between the microsystem and the external instrumentation will be used.

Detailed description of the drawings

Figure 1 shows the needle with the sensors.

Figures 2 to 15 illustrate the primary stages in the manufacturing process of the chemical sensors in the lancets.

Figure 16 shows a sketch of a possible model of the impedance measuring circuit, including stimulation and measurement. Figure 17 is a model of the sinusoidal stimulation circuit. Figure 18 shows the detail of the AC generator in figure 17. Figure 19 shows the detail of the BFP and Output Buffer in figure 17. Figure 20 is a model of the measurement circuit. Figure 21 is the detail of the module and phase measurement in figure 20. Figure 22 is the detail of AD converter in figure 20.

Model of the invention

The system is designed and optimized for applications in the medical field. Specifically, its use is for tissue characterization and monitoring by inserting the system in a tissue, organ or body fluid. The physical-chemical parameters to be recorded can vary depending on the specific application. Initial parameters, which are considered standard, are temperature, pH, and K and tissue impedance.

One of the uses of this invention is to insert the lancet to measure myocardial tissue impedance, as well as measure H+ and K+ ion concentration for application during open-heart surgical operations during which the electrocardiogram cannot provide any information regarding the tissue status or its evolution.

Other specific applications identified

- Monitoring cardiac tissue during experimentally provoked cardiac ischemia.
- Monitoring cardiac tissue online during extracorporeal surgery.
- Monitoring the tissue of any organ during conventional surgery.
- Monitoring the tissue of any organ during minimally invasive surgery.
- Monitoring and characterizing skeletal muscle metabolism.
- Online monitoring during the transport of organs for

transplant.

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- Online monitoring of transplanted organ rejection evolution.
- Online monitoring and characterizing of other tissues: brain, liver.
- Online monitoring and characterizing of tumorous tissues.
- Online monitoring and characterizing of body fluids.
- Monitoring and characterizing food preservation status.
- Monitoring and characterizing the environment.

[5] Numbers in the margin indicate pagination in the foreign text.

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CLAIMS

1. Microsystem which is distinct because it integrates one or more sensors in a silicon substratum has reduced dimensions, approximately millimeters, and the shape of a needle. It also includes a preprocessing and signal amplification circuitry and a telemetry circuitry to transmit data a short distance.

2. Microsystem according to claim 1 in which one of more of the sensors are type ISFET for measuring analytes.

3. Microsystem according to claim 1 in which one or more of the sensors are electrode sets for measuring impedances at four levels.

4. Microsystem according to claim 1 in which one or more of the sensors are metal resistors to measure temperature.

5. Microsystem according to claim 1 which is distinct because it is shaped like a needle which enables it to be inserted into and extracted from biological tissue or other materials. The sensors are located in the area that will be inserted in the tissue or material to be analyzed.

6. Microsystem according to claim 1 which is distinct because it is made with biocompatible materials or biocompatible coated systems for certain components.

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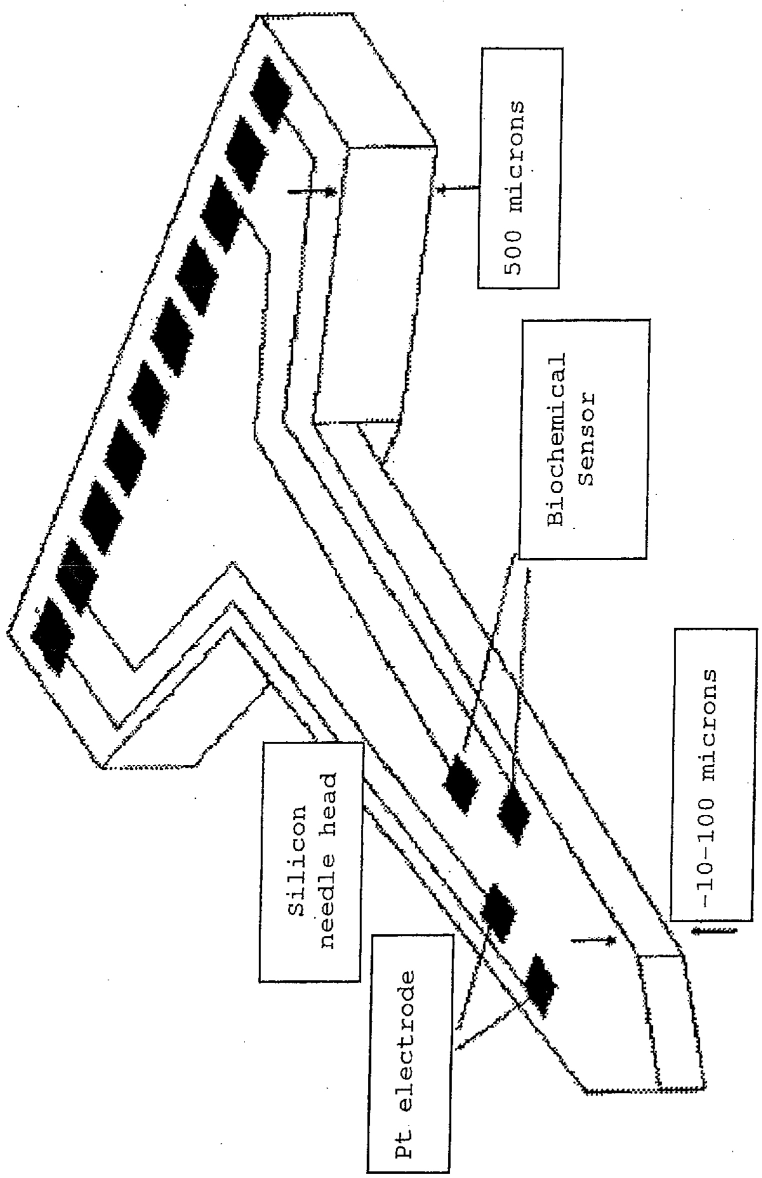

Figure 1

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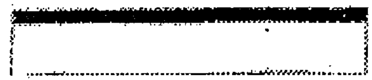


Fig. 2

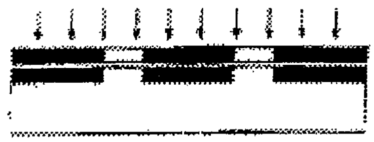


Fig. 3

Fig. 4

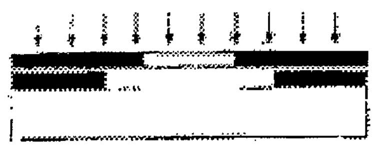
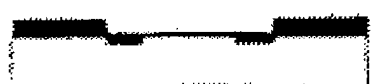


Fig 5



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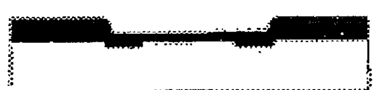

Fig. 7

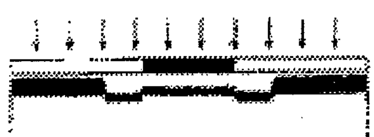

Fig 8

[8] Numbers in the margin indicate pagination in the foreign text.

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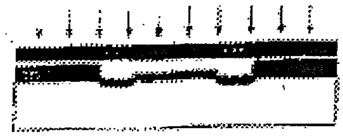

Fig. 9

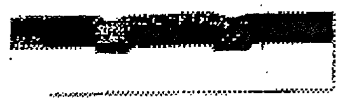

Fig. 10

Fig. 11

Fig 12

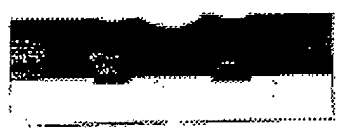

Fig. 13

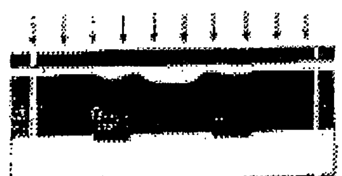

Fig. 14

Fig. 15

[9] Numbers in the margin indicate pagination in the foreign text.

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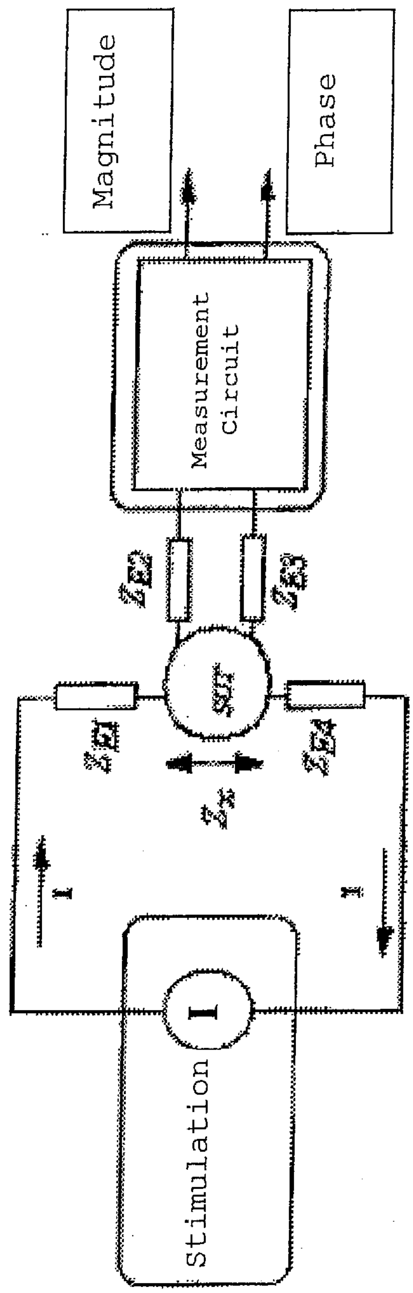

Figure 16

[10] Numbers in the margin indicate pagination in the foreign text.

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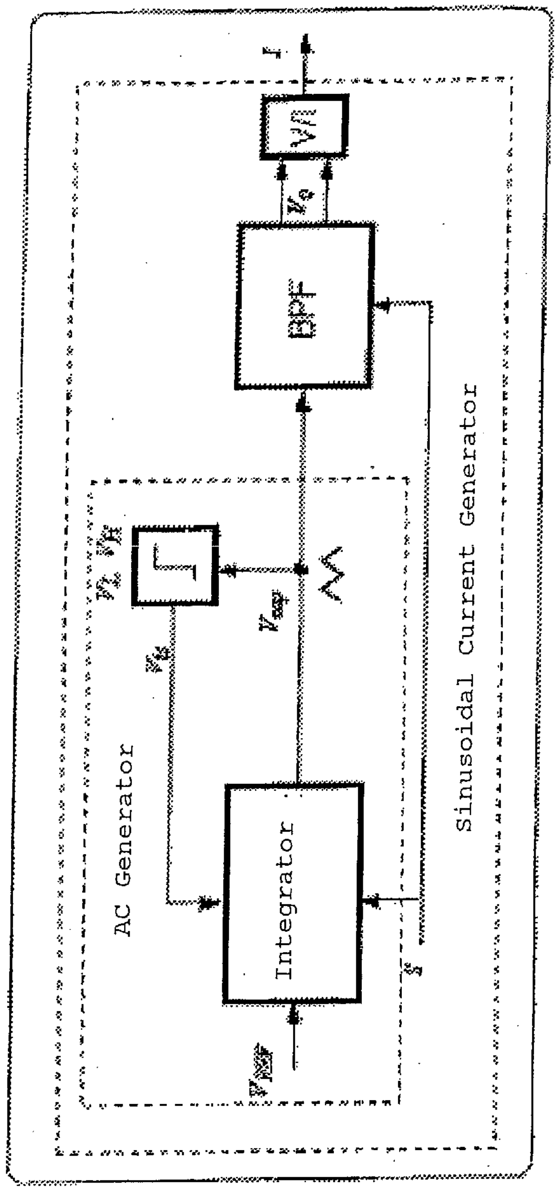

Figure 17

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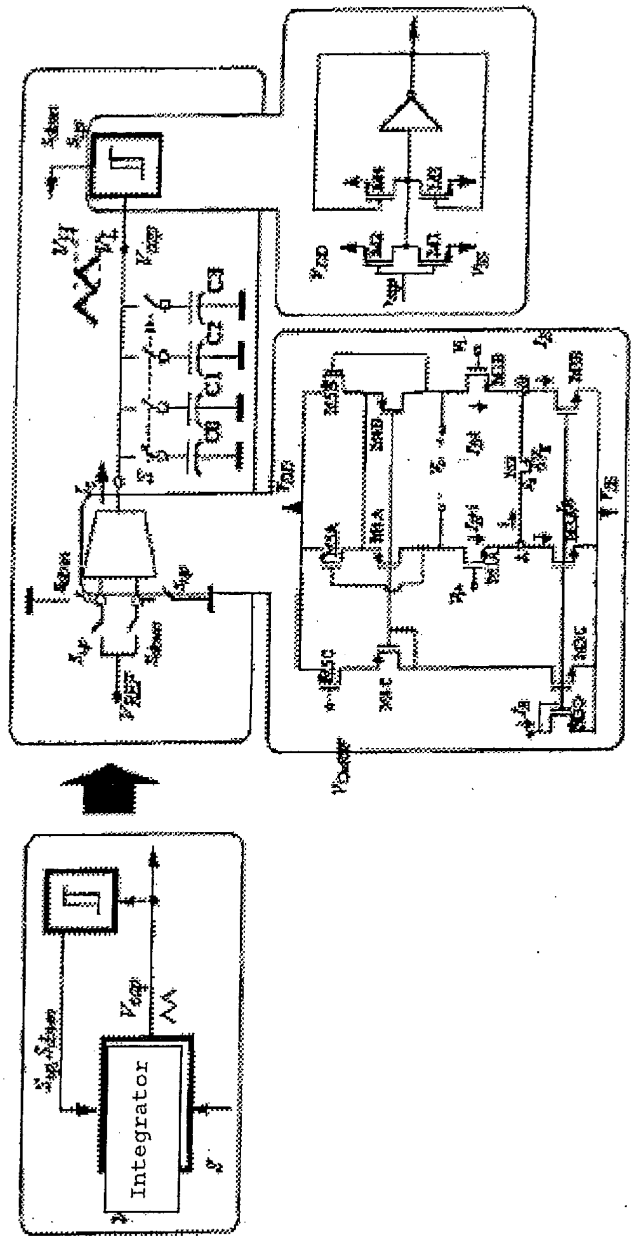

Figure 18

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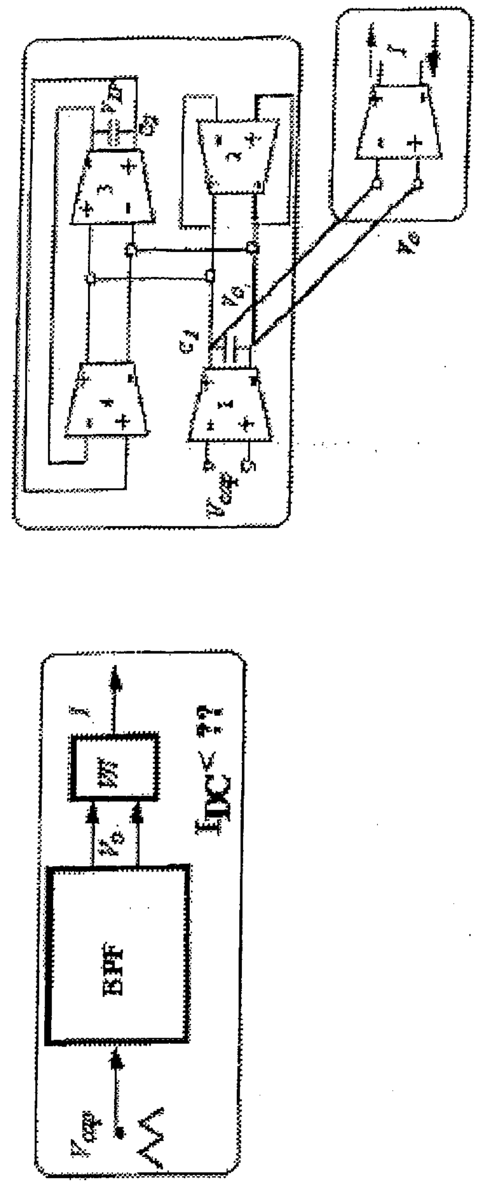

Figure 19

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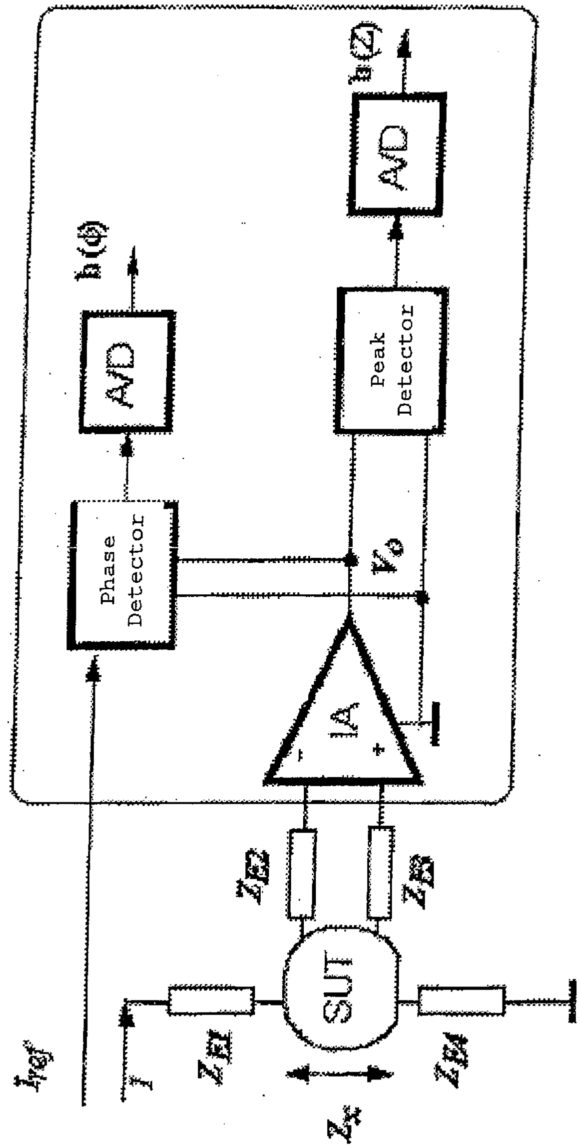

Figure 20

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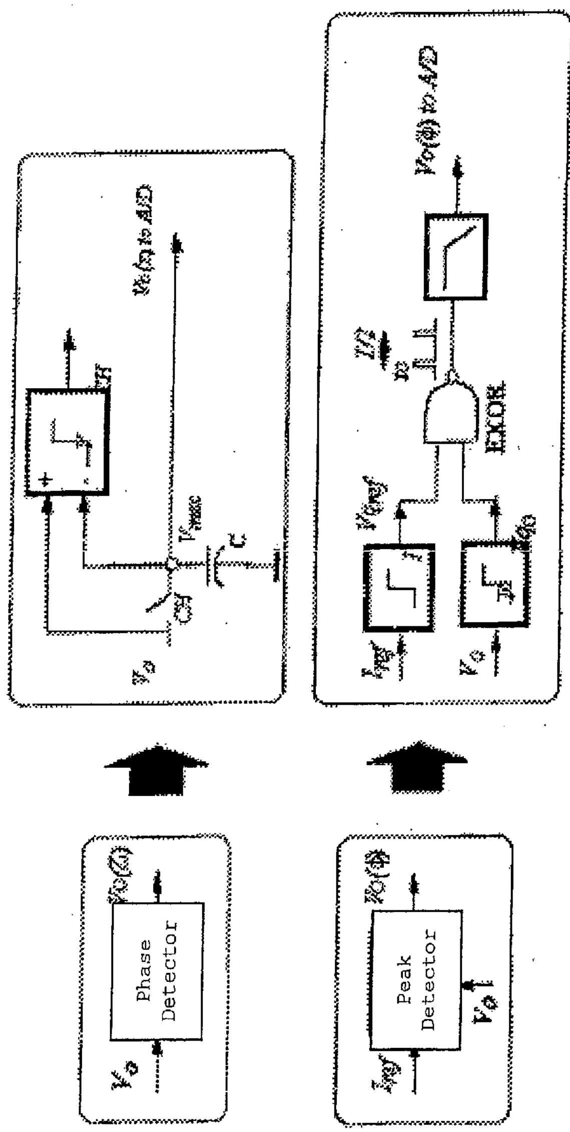

Fig. 21

Figure 21

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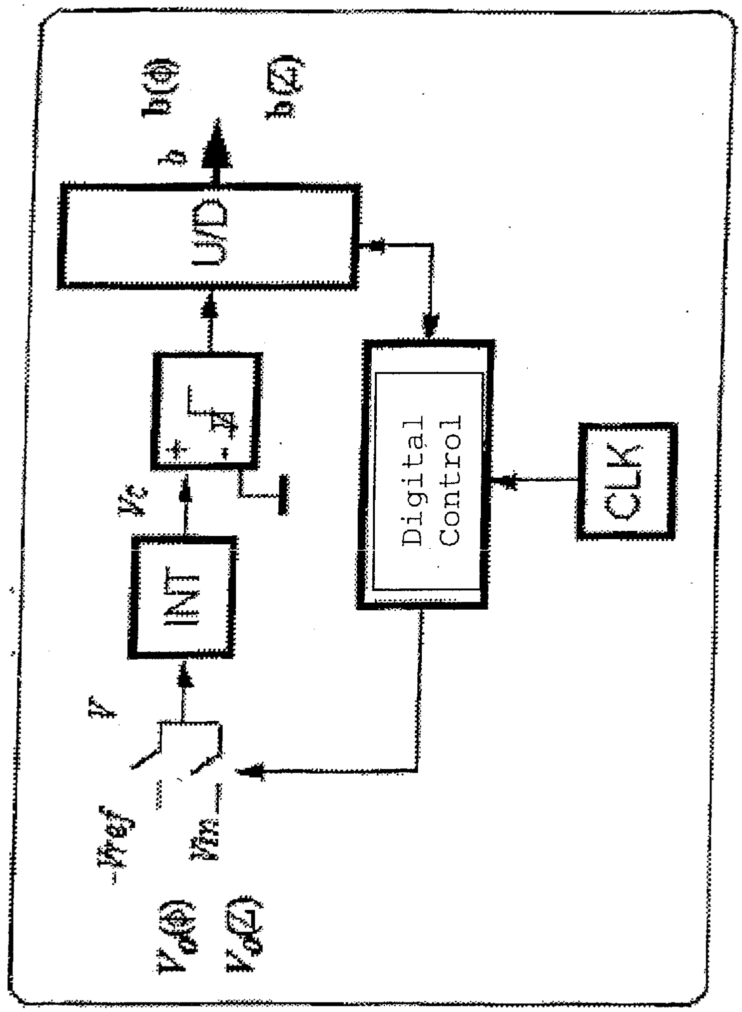

Figure 22

[16] Numbers in the margin indicate pagination in the foreign text.

CITED LITERATURE

Category	Documents Cited	Claims Affected
X Y	US 4874500 A (MADOU et al) 17.Oct.1989, entire document	1 3 – 5
A	EP 01298952 A2 (KURARAY CO. LTD), 02.Jan.1985, entire document	1 – 6
X Y	US 5068205 A (BAXTER et Al) 26.Nov.1991, entire document	1 2
Y	US 4505799 A (BAXTER) 19.Mar.1985, entire document	2
Y	PATENT OF ABSTRACTS OF JAPAN, CD-ROM Vol. 52, JP 02-099853 A (HITACHI LTD) 11.Apr.1990, summary, figures 1, 2	3
Y	US 5394883 A (NEUMAN 07.Mar.1995, entire document	4
Y	US 4407294 A (VILKOMERSON) 04.Oct.1983, entire document	5
X	US 5846392 A (KNOLL) 08.Dec.1998, entire document	1.6

Category of documents cited

X: specific relevance
Y: specific relevance combined with other/s of the same category
A: reflects technology status

O: reference to unwritten disclosure
P: published between the priority date and submission of application
E: previous document, but published after submission of application

This report was prepared for
☒ All claims

☐ Claim Numbers:

Report Date:
23. Feb.2001

Examiner:
M. Fluvia Rodriguez

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